

The invention relates in part to assay methods that utilize water soluble hybrid phthalocyanine derivatives as fluorescent labels. The water soluble hybrid phthalocyanine derivatives of the instant invention have advantageously large stokes shifts and intensities, and are useful as labels, for example in assays for determining the presence or amount of an analyte in aqueous samples.

Claims 23-35 are presently pending in the instant application, and claims 28, 30, 32, and 34 are under consideration by the Examiner. Applicant respectfully requests reconsideration of the claimed invention in view of the following remarks.

Non Art-Related Remarks

35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 28, 30, 32, and 34 under 35 U.S.C. § 112, second paragraph, contending that the claim is indefinite for reciting "ligand analogue." Applicants respectfully traverse this rejection.

When determining definiteness, the proper standard to be applied is "whether one skilled in the art would understand the bounds of the claim when read in the light of the specification." *Credle v. Bond*, 30 USPQ2d 1911, 1919 (Fed. Cir. 1994). See also *Miles Laboratories, Inc. v. Shandon, Inc.*, 27 USPQ2d 1123, 1127 (Fed. Cir. 1993) ("If the claims read in the light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more.") (emphasis added).

The phrase "ligand analogue," as used in the instant claims, is commonly used by the ordinarily skilled artisan to refer to molecules that are capable of binding to a binding partner for a target ligand, but that may differ slightly in composition from the target ligand. For example, the instant claims describe assays for measuring the presence or amount of a target ligand, using a ligand analogue conjugate "comprising at least one ligand analogue... whereby said ligand analogue conjugate competes with said target ligand for binding to [a] ligand receptor." See, e.g., claim 28(a).

This usage of the phrase is fully consistent with the ordinary definitions of “ligand” and “analogue” that are well known to the artisan (*see, e.g.*, Dictionary of Cell Biology, Second Edition, Academic Press, San Diego: ligand -- any molecule that binds to another; Merriam Webster’s Collegiate Dictionary, 10th Edition: analogue -- something that is analogous or similar to something else); as well as the common usage of the phrase in the art (*see, e.g.*, U.S. Patent No. 5,391,483, column 1, lines 29-33: “In competitive binding assays, a labeled ligand analog (sometimes referred to as ligand analog herein) is placed in competition with the unlabeled ligand for reaction with a fixed amount of the appropriate binding material.” U.S. Patent No. 5,143,852, column 2, lines 21-29 “Heterogeneous, competitive ligand-receptor assays require a separation of ligand analogue conjugate bound to ligand receptor from the free ligand analogue conjugate and measurements of either the bound or the free fractions. Methods for performing such assays are described in U.S. Pat. Nos. 3,654,090, 4,298,685, 4,425,438, and 4,506,009, European Patent Application 87309724.0, and PCT International Application No. PCT/US86/00668.”).

Therefore, due to its common usage by ordinarily skilled artisans, Applicant respectfully submits that one skilled in the art would reasonably understand the bounds of the phrase “ligand analogue.” Accordingly, because this phrase meets the standard of 35 U.S.C. § 112, second paragraph, Applicant requests that the Examiner withdraw this rejection.

Art-Related Remarks

35 U.S.C. § 103

The Examiner has rejected claims 30 and 34 under 35 U.S.C. § 103(a) as being unpatentable over Margaron *et al.*, J. Photochem. Photobiol. B 14: 187, in view of Renzoni *et al.*, U.S. Patent No. 5,627,028, in further view of Freytag, U.S. Patent No. 4,434,236. The Examiner has also rejected claims 28 and 32 as being unpatentable over Margaron *et al.*, in view of Renzoni *et al.*, and Freytag, and in further view of Stanton *et al.*, U.S. Patent No. 4,803,170. Applicant respectfully traverses these rejections.

To establish a prima facie case of obviousness, three criteria must be met: there must be some motivation or suggestion, either in the cited references or in knowledge available to one skilled in the art, to modify or combine the cited references; there must be a reasonable expectation of success in combining the references to achieve the claimed invention; and the references must teach or suggest all of the claim limitations. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 2143.

The instant claims describe methods for determining the presence or amount of a target ligand, by detecting a signal from a ligand analogue conjugate comprising a water soluble hybrid phthalocyanine derivative in which at least one of the four pyrrole moieties is fused to a single carbocyclic ring. *See, e.g.*, claim 28. As discussed above, the water soluble hybrid phthalocyanine derivatives of the instant invention can provide fluorescent conjugates exhibiting advantageously large stokes shifts and fluorescence intensities.

Margaron et al.

In contrast, the Margaron *et al.* reference discloses the use of phthalocyanine derivatives in cancer phototherapy. In phototherapy, such phthalocyanine derivatives may be useful, not because of any advantageous fluorescent properties, but because such molecules (i) may be more selectively absorbed and retained by cancer tissues; (ii) may be more readily eliminated by non-target tissues; and (iii) can readily absorb light towards the red end of the physical spectrum, allowing the use of a light wavelength that penetrates deeper into tissue. *See Margaron et al.*, pages 187-188. Furthermore, usefulness in cancer phototherapy depends on the generation of singlet oxygen, which is toxic to cells, by the photosensitizing molecule, and not on fluorescence of the molecule. *See, e.g.*, Margaron *et al.*, page 196, last four lines.

Referring to the Margaron *et al.* reference, the Examiner contends that “[t]he compounds have superior absorption properties due to the perturbation of the (na)phthalocyanine D_{4h} symmetry and the modification of the accennalation” (Paper No. 9, page 4). First, the Margaron *et al.* reference does not support the Examiner’s contention. In fact, the Margaron *et al.* reference actually states that “[b]ecause of the perturbation of the (na)phthalocyanine D_{4h} symmetry and

the modification of the accennalation, the degree of sulfonation of the different condensation products can readily be deduced.” Margaron *et al.*, page 188, second full paragraph (Emphasis added). This statement says nothing concerning any “superior absorption properties” of the disclosed molecules.

Moreover, as discussed above, any “properties” of the phthalocyanine derivatives disclosed the Margaron *et al.* reference, such as the fact that they may be absorbed by cancer tissues and produce singlet oxygen, are only relevant to the use of the dyes in cancer therapy, and not to the assay methods of the instantly claimed invention. In fact, the Margaron *et al.* reference is silent as to the fluorescence properties of such phthalocyanine derivatives, or to any other advantages that are relevant to the instantly claimed assay methods. Furthermore, the Margaron *et al.* reference actually teaches away from using water soluble molecules, as required by the instant invention, stating that amphiphilic molecules are superior to hydrophilic molecules in phototherapy applications. *See, e.g.*, Margaron *et al.*, page 197, lines 2-4.

Renzoni et al.

The Examiner continues by contending that “Renzoni et al. teach water-soluble phthalocyanine derivatives that read directly on those of the instant claims.” Paper No. 9, page 4. Again, the Renzoni *et al.* reference does not support the Examiner’s contention. As discussed in Applicant’s previous response, the Renzoni *et al.* reference does not disclose or suggest any hybrid phthalocyanine derivatives, as required by the instant claims. Instead, the Renzoni *et al.* reference discloses only phthalocyanine molecules in which each pyrrole moiety is fused to a single aromatic ring. *See, e.g.*, Renzoni *et al.*, abstract; Figure 1; column 3, lines 34-51.

The prima facie case

The Examiner then attempts to combine the Margaron *et al.* reference and the Renzoni *et al.* reference, contending that the use of the phthalocyanine derivatives disclosed by Margaron *et al.* in conjugates as disclosed by Renzoni *et al.* would be obvious. But, as discussed above, there must be some motivation or suggestion, either in the cited references or in knowledge available to one skilled in the art, to combine the cited references and produce the claimed invention. Here,

no such motivation has been demonstrated by the Examiner. There is nothing in the Margaron *et al.* reference suggesting that the disclosed phthalocyanine derivatives would be of any use in conjugates or in assay methods, and the Margaron *et al.* reference even teaches away from using water soluble molecules in the disclosed (and unrelated) cancer phototherapy applications. Moreover, there is nothing in the Renzoni *et al.* reference to suggest that properties rendering molecules useful in cancer phototherapy would make those molecules useful as conjugates for use in assays. Accordingly, there is no motivation or suggestion to the skilled artisan to select, from amongst all possible phthalocyanine derivatives, water soluble hybrid phthalocyanine derivatives in which at least one of the four pyrrole moieties is fused to a single carbocyclic ring, as required by the instant claims, for use as a fluorophore in an assay for a target ligand. Thus, no *prima facie* case of obviousness has been established by the Examiner.

Finally, neither the Freytag reference, nor the Stanton *et al.* reference, discloses or suggests any phthalocyanine molecules whatsoever, nor does the Examiner contend that either reference does so. Instead, these references are cited merely as describing assay methods generally. Thus, these secondary references do not overcome the deficiencies of the Examiner's faulty *prima facie* case of obviousness.

Therefore, instead of carrying the burden of establishing a *prima facie* case of obviousness, the Examiner has engaged in "...decomposing an invention into its constituent elements, finding each element in the prior art, and then claiming that it is easy to reassemble these elements into the invention...". *In re Mahurkar*, USPQ2d 1801, 1817 (N.D. Ill. 1993). An obviousness determination cannot be premised on such an impermissible use of hindsight. See *In re Fine*, 5 USPQ2d 1596 1600 (Fed. Cir. 1988) ("To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against the teacher.")

Accordingly, because the references cited by the Examiner, alone or in combination, fail to disclose or suggest the instantly claimed methods, no *prima facie* case of obviousness has

been established. Therefore, Applicant respectfully requests that the Examiner withdraw the rejection.

CONCLUSION

In view of the foregoing remarks, Applicant respectfully submits that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

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